AUA
VOLUME 41 UPDATE SERIES LESSON 5
2022

Fertility Considerations in Pediatric and Adolescent Urology

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to list the most common threats to fertility in children and adolescents and to enumerate the initial steps in fertility preservation.

This AUA Update aligns with the American Board of Urology Module on Impotence, Infertility and Andrology. Additional information on this topic can be found in the AUA Core Curriculum sections on Infertility and Pediatric Urology.

Kathleen Kieran, MD, MS, MME, FACS, FAAP[1,2] and Margarett Shnorhavorian, MD, MPH, FACS, FAAP[1,2,*]

[1]Division of Urology, Seattle Children's Hospital, Seattle, Washington

[2]Department of Urology, University of Washington, Seattle, Washington

*Supported by Grant 1R01CA17521601A1 from the National Institutes of Health and National Cancer Institute.

All other authors: nothing to disclose.

American Urological Association

Accreditation: The American Urological Association (AUA) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation: The American Urological Association designates this enduring activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

KEY WORDS: pediatric, fertility, differences in sexual differentiation, oncology, cryptorchidism

INTRODUCTION

Infertility is the inability to conceive a viable pregnancy after 1 year (6 months if the female partner is aged ≥35 years) of regular sexual intercourse without contraception.[1] Thus, patients with infertility typically present after a prolonged period of difficulty conceiving or carrying a viable pregnancy to term. The diagnosis and treatment of patients with infertility centers not only on the identification (and anticipated correction) of structural and functional abnormalities precluding conception and viable pregnancy, but also on preventing fertility loss or proactively identifying risk factors for decreased fertility potential before attempting conception. Improved understanding of the anatomical, physiological and pharmacological factors that threaten fertility has made it clear that fertility concerns are not limited to patients attempting to conceive, but rather include all patients at risk for developing these conditions. In many cases, these risk factors for decreased fertility potential exist in childhood; however, providers are not universally confident in managing fertility concerns with pediatric patients and families.[2] Fertility concerns are often time-sensitive, and so missed opportunities to discuss fertility preservation with patients and families can have long-lasting ramifications. Thus, both pediatric and adult urologists must be familiar with the most common pediatric conditions associated with decreased fertility potential and the options to maximally preserve fertility, and to facilitate referral to an infertility specialist when needed.

Decreased fertility may result from endocrine disorders of the hypothalamic-pituitary-gonadal (HPG) axis (fig. 1), variations in end-organ hormonal sensitivity, structural abnormalities in the reproductive organs, altered function of the reproductive organs or any combination thereof. The evaluation and management of patients with decreased fertility potential is ideally undertaken in a multidisciplinary setting prioritizing the patient's goals and expectations; however, urologists are often called on early in the evaluation of these patients. In this Update, we present the most common pediatric causes of altered fertility potential relevant to urologists (summarized in table 1).

CAUSES

Pediatric cancer and its treatments. As survival rates for pediatric cancers have increased, refinements of oncologic care in children have centered on preservation of quality of life and organ function. Acknowledgment of the potential for and efforts to minimize loss of fertility may contribute to the emotional and social well-being of childhood cancer survivors.[3–6] Barriers to fertility in patients with cancer can be hormonal (eg changes in the function of the HPG axis or sensitivity of the end organ) or structural (eg altered anatomy precluding normal function or direct cytotoxicity of spermatogonial stem cells).[4] In one study, 1 in 4 survivors of childhood cancer and 1 in 3 survivors of testicular cancer had elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) consistent with hypergonadotropic hypogonadism.[5] Hormonal deviations along the HPG axis can arise after treatment with chemotherapy, most notably with alkylating agents such as busulfan, chlorambucil and cyclophosphamide. **Alkylating agents are associated with gonadal damage at rates 4 times that of other chemotherapeutic agents.**[6] Although alkylating agents are known to have direct and dose-dependent toxic effects on testicular tissue, they are relatively infrequent in contemporary chemotherapeutic regimens; the effects of platinum-based chemotherapies and ifosfamide, both common in current chemotherapy regimens, are much less well-studied, but bleomycin has been associated with impaired fertility.[7] While studies of patients receiving ifosfamide and/or cisplatin are limited in scope and quality,[8] one study found lower pregnancy rates in patients receiving chemotherapy compared with sibling controls, suggesting that fertility concerns are warranted in this population.[9]

Patients undergoing stem cell transplantation (SCT), especially in conjunction with myeloablative regimens (especially those involving whole-body radiotherapy), are likely to experience fertility loss; only 1 in 3 women had successful pregnancies after nonmyeloablative SCT, while premature ovarian failure (loss of ovarian function prior to age 40)[10] was very common in patients receiving myeloablative regimens.[11] Adults also report functional changes such as erectile dysfunction and decreased vaginal lubrication following SCT.[12]

In males, the germinal epithelium of the testis is much more sensitive to cytotoxic agents than are the Leydig cells,[13] so disruptions in spermatogenesis are historically much more common than disruptions in steroidogenesis. Testicular cancer survivors who received multiple cycles of platinum-based chemotherapy are 17 times as likely to develop hypogonadism.[5] **While hypogonadism developing after chemotherapy is not clearly dose-dependent,[14] hypogonadism after radiation therapy appears to be ≥24 Gy in prepubertal patients and ≥30 Gy in postpubertal patients.** Nearly all patients receiving platinum-based chemotherapy at cumulative doses ≤600 mg/m^2 had at least 10 million sperm/cc, compared with fewer than 50% of patients receiving higher doses.[15]

Differential methylation of specific DNA loci is a normal part of germ cell development.[16] Variability in methylation patterns is associated with lower sperm counts and clinically decreased fertility.[17] Hypermethylation and hypomethylation have been observed in humans and animals following exposure to multiple antineoplastic agents; the persistence of these novel patterns in future generations suggests that chemotherapy may effect epigenetic shifts via differential spermatozoal methylation.[18]

The ovary is also highly sensitive to the effects of chemotherapy, especially alkylating agents. Unlike spermatogenesis, additional oocytes do not develop after birth.[19] Options for fertility preservation in females include oocyte and ovarian tissue cryopreservation.[20] While the former avoids resection of gonadal tissue, harvesting oocytes necessitates ovarian stimulation, which requires several weeks and thus may delay treatment. The latter avoids these issues, but since ovarian tissue

ABBREVIATIONS: uroflowmetry (UF), urinary tract infection (UTI)

is harvested "as is," follicles may not be mature and neoplastic cells may be preserved. Additional fertility considerations in women include the integrity of the fallopian tubes, uterus and vagina, which may be damaged by pelvic surgery and radiation therapy.[21]

In addition to direct end-organ effects, childhood cancer survivors may develop hypogonadotropic hypogonadism or precocious puberty (secondary sexual characteristics before age 9).[22] Children who underwent intracranial surgery or received cranial radiotherapy at cumulative doses >30 Gy are at greatest risk for hypogonadotropic hypogonadism.[23] Children receiving cranial irradiation at cumulative doses exceeding 18 Gy are at highest risk for precocious puberty.[24]

Urologists commonly care for patients with testicular cancer, in whom orchiectomy followed in some cases by radiation therapy and/or chemotherapy may confer increased risk of fertility challenges. Even before treatment, males with testicular cancer may have abnormal semen parameters. Thus, it is critical that these men undergo counseling on fertility preservation even before orchiectomy is undertaken.

Nononcologic conditions treated with gonadotoxic therapy. Many nononcologic medical conditions, including organ transplantation and rheumatological diseases, are commonly treated with drugs that adversely affect fertility potential.[25] In addition, the underlying medical conditions may have direct deleterious effects on fertility. **Liver and kidney disease, particularly end-stage, are also associated with HPG axis derangements, with axis normalization typically returning approximately 1 year after transplantation.**[26] About 25%–50% of women with rheumatoid arthritis meet the criteria for infertility;[27] these women may enter menopause earlier and may have higher levels of anti-müllerian hormone than women without rheumatoid arthritis.[28] Patients with inflammatory bowel disease (IBD) can also have decreased fertility, either because of surgery (eg sexual dysfunction after proctocolectomy or pouch surgery) or because of the disease itself. Abnormal fertility is more common in patients with IBD during disease flares,[29] and among women with IBD those who have undergone surgery are nearly 4 times as likely to experience infertility compared to those who have not (though this relationship is associative, not causal).

The relative contributions of rheumatological diseases and their treatments to alterations in fertility can be difficult to distinguish: during disease flares, women are more likely to have abnormal serum hormone levels, but are also less likely to engage in sexual activity and to take drugs that may impact fertility.[28] Men with active IBD are more likely to experience erectile dysfunction than those whose disease is in remission.[30] As such, maximizing fertility potential in patients with these conditions centers on optimizing disease control including quality of life and normal activity levels by minimizing disease flares, balanced with the minimum necessary exposure to drugs that may impair fertility. Clinicians caring for patients with chronic diseases should also be cognizant of the spectrum of disease that each patient might experience (eg severe fatigue, concomitant arthritis) as well as the side effects of pharmacological (eg striae or weight gain related to steroid use) and surgical (eg abdominal stoma) treatments that may alter a patient's self-image or self-confidence.[30]

Many drug classes (eg alkylating agents) used to treat rheumatological conditions are also used for cancer treatment and are discussed above. **High-dose nonsteroidal anti-inflammatory agents decrease prostaglandin production by blocking cyclooxygenase enzymes; prolonged nonsteroidal anti-inflammatory use is associated with normal serum hormone levels but decreased sperm count and motility.**[28] In contrast, corticosteroids appear to directly affect the HPG axis, but without consistent effect on semen parameters.[31] Other common immunomodulatory medications (eg methotrexate, chloroquine and tumor necrosis factor-alpha inhibitors) have not shown predictable changes in semen parameters.[32] Although the medications for cancer and autoimmune diseases may be similar, findings from each group of patients should not be considered directly translatable to the other, as the underlying pathophysiology and treatment regimens differ. For example, patients undergoing SCT for autoimmune rather than oncologic disease fared much better: 36% of women with autoimmune disease had successful pregnancies and none experienced premature gonadal failure.[33] In contrast, only 22% of women undergoing SCT had return of regular (cyclic) menses, with younger patients and those in better overall health being more likely to resume menstrual cycles.[34] However, likelihood of premature birth remained elevated in the children of women who had undergone SCT.[34]

There is a relative paucity of literature on fertility preservation in adolescents with rheumatological and other autoimmune diseases. Although adolescent and young adult women with rheumatological diseases are interested in discussing reproductive health, they were dissatisfied with the frequency and content of these conversations and indicated that rheumatology providers were not a high-quality source of information about sexual and reproductive health.[35] Unfortunately, previous work supports these findings: in 1 series, more than half of patients received no counseling on fertility preservation, and only 1 in 4 males were offered the opportunity to bank sperm. Women who were offered fertility preservation reported that they were provided limited options (eg only leuprolide acetate). These findings underscore the need to elicit patient preferences and knowledge around fertility and to comprehensively explore the available options.[36]

Cryptorchidism/limited testicular reserve. Between 1% and 4% of term and 30% and 45% of premature male infants have an undescended testicle (UDT) at birth.[37] Most UDTs will descend spontaneously early in life, with about 1% of males having persistent cryptorchidism at 1 year of age.[37] **UDTs have fewer germ cells and are smaller in size compared with normally descended testicles, with decreased production of dark (type Ad) spermatogonia from gonocytes.**[37] This decrease in type Ad spermatogonia is correlated with variations in sperm concentrations and motility on semen analysis. Among patients with unilateral cryptorchidism, patients with decreased concentrations of type Ad spermatogonia had normal serum FSH levels and normal sperm concentration and motility, but the FSH levels were significantly higher and semen parameters significantly worse than in patients with normal concentrations of type Ad spermatogonia, despite all parameters being within the "normal" range. In contrast, in patients with bilateral UDTs, serum FSH levels and sperm motility were similarly decreased in the groups with low and

normal concentration of type Ad spermatogonia, although the sperm counts were lower in patients with a lower concentration of type Ad spermatogonia. Unilateral and bilateral UDTs may be associated with differential sensitivity to the development of endocrinopathy, and it has been proposed that type Ad spermatogonia concentration may be a more sensitive marker of decreased fertility potential compared with germ cell concentration, serum hormone levels or semen parameters.[38]

The American Urological Association published a Guideline on the Evaluation and Treatment of Cryptorchidism in 2014 (available at https://www.auanet.org/guidelines/cryptorchidism-guideline). **Early orchiopexy (as soon as safely feasible given anesthetic considerations and the child's overall health, and ideally by 1 year of age) is currently recommended to maximally preserve fertility.** Hormonal treatment with human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone (GnRH), historically an option for the nonsurgical management of cryptorchidism, is formally not recommended. Patients who are older at the time of orchiopexy are more likely to have abnormal FSH and LH levels and semen analyses as adults.[39] It is important for clinicians to recognize that the favorable fertility outcomes associated with early orchiopexy apply predominantly to otherwise healthy children; young boys with other syndromes associated with changes in fertility (eg Prader-Willi, Klinefelter syndromes) may still require medically assisted reproduction or medical therapy to maximize fertility.[40]

Varicocele. A varicocele (fig. 2) is a dilatation of the veins of the pampiniform plexus. Although varicoceles remain rare (<1% prevalence) in prepubertal boys, up to 1 in 3 pubertal boys will develop a varicocele.[41] **The drainage of the left gonadal vein into the left renal vein creates increased hydrostatic pressure, making varicoceles more common on the left side.** The effect of varicoceles on fertility appears to be multifactorial. The increased volume of blood present around the testicle in the setting of dilated veins is associated with local increases in testicular temperature both ipsilaterally and contralaterally, as well as markers of oxidative stress. Locally increased testicular temperature associated with varicoceles has been associated with changes in semen parameters, notably sperm morphology and motility.[42]

More than 1,000 peer-reviewed manuscripts are published on the topic of varicoceles in adolescents. Despite this, there is not a consensus on when and in whom to operate. Although higher grade (grade 3) varicoceles are associated with worsened semen parameters compared with grade 1 or 2 varicoceles (table 2), there is not a direct correlation between semen parameters and clinical fertility or lack thereof in these patients. Similarly, there is no consensus regarding the relationship between varicocele grade and testicular growth in adolescents.[43] The current American Society for Reproductive Medicine recommendations for varicocele repair are a clinically palpable varicocele associated with abnormal semen parameters and–in adults–an inability to conceive after 1 year of unprotected intercourse, with no uncorrectable fertility concerns in the female partner.[44] In adolescents, testicular size is correlated with sperm production, and thus substantial (≥20%) and persistent discrepancies in testicular size are often considered indications for repair. However, adolescent patients with less pronounced (>10%) asymmetry may have "catch up" growth of the affected testis after varicocelectomy.[45] Testicular size can be assessed using physical examination, orchidometers or sonography; while the last is most objective, it is also costly. Additionally, what constitutes "persistent" testicular size discrepancy is not well defined, especially since transient asymmetry can be seen with normal pubertal development.

Although the prolonged interval between diagnosis and paternity for varicoceles diagnosed in adolescents may confound the relationship between surgical intervention and potential improvements in fertility, a study of 408 adolescents with palpable varicoceles followed for 16 years found that a larger proportion of those who underwent microsurgical varicocelectomy were fertile (77.3% vs 48.4%), with shorter time to conception (mean 11.2 vs 16.9 months).[46] However, this study was not randomized. The published peer-reviewed literature on adolescent varicoceles has few randomized studies and a predominance of meta-analyses, with inconsistent recording of Tanner stage, objective testicular measurements and semen analyses; thus, although some studies support early intervention to preserve or improve fertility in adolescents, whether and when to operate on varicoceles in adolescents remains controversial.

While semen analyses are consistently collected in the evaluation of adults with varicoceles, only about 12% of pediatric urologists regularly collect semen samples from patients with varicoceles; lack of patient/family and provider comfort with the procedure, as well as lack of patient and family knowledge about the procedure were cited as the main reasons that semen analyses were not routinely performed.[47] Another barrier to using semen analyses in clinical decision making for adolescent patients with varicoceles is the lack of standardized normal semen parameters in teenagers. The reference values for semen parameters set forth by the World Health Organization were collected from men whose partners were able to conceive in 12 or fewer months and thus did not meet the criteria for infertility. Although several manuscripts have described semen characteristics in adolescents (including 1 paper finding that over 75% of adolescents with varicocele and symmetrical testes had semen parameters within the ranges defined by the World Health Organization),[48] and published data suggest that surgical repair is associated with improvement in semen analyses for adolescents in some series, there are not presently standard values for semen analyses in this age group.

Although most publications on varicoceles have focused on the correlation between testicular size and semen parameters, relatively few studies have assessed the role of testosterone in the presentation and outcome of patients with varicoceles. Although improvements in serum testosterone levels before and after surgical correction of the varicocele have been reported in some studies, to date no studies have definitively and consistently shown a correlation between the presence (or severity) of a varicocele and serum testosterone level, and very few studies report serum testosterone levels at all in men with varicoceles. At least 1 study found that serum testosterone levels were normal in young men (median age 19 years) with varicoceles, although, in comparison to men without varicoceles, these patients were more likely to have lower levels of inhibin-B and elevated FSH and LH, as well as poorer semen parameters, especially in higher-grade varicoceles.[49]

Differences in sex development (DSD). Patients with DSD have a congenital condition associated with atypical chromosomal, gonadal or anatomical sex. DSD may occur at the chromosomal level (eg Klinefelter [47,XXY] or Turner [45,XO] syndromes; discussed elsewhere), or when tissue has altered hormonal receptivity (eg partial or complete androgen insensitivity). **Patients with complete androgen insensitivity syndrome (CAIS) are phenotypically female, with blind-ending vaginas and no müllerian structures. The testes in these patients have hyperplastic Leydig cells, local fibrosis and low numbers of type Ad spermatogonia.**[50] Patients with CAIS typically undergo gonadectomy after puberty, so fertility counseling should be performed prior. Patients with partial androgen insensitivity syndrome and 5-alpha reductase deficiency may present with more phenotypic variation based on the degree of virilization. In these patients, the integrity of the wolffian structures and of spermatogenesis may inform a patient's likelihood of fertility. Like patients with CAIS, patients with partial androgen insensitivity syndrome may undergo gonadectomy after puberty given the risk of malignant transformation.

In ovotesticular DSD, patients have both ovarian and testicular tissue, either in the same gonad (ovotestis) or with an ovary on one side and a testis contralaterally. Although most children with ovotesticular DSD are reared as males, ovulation is possible.[51] These patients may be fertile if the internal genitalia are functional, although gonadectomy to prevent development of gonadoblastoma may render patients infertile.

46,XY DSD males may be undervirilized with defects in testosterone synthesis or when Leydig cells are absent or nonfunctional. These patients are usually infertile, although hCG stimulation can be considered if Leydig cells are present.[52]

Congenital adrenal hyperplasia. Congenital adrenal hyperplasia is an autosomal recessive condition caused by a loss of 21-hydroxylase or (less commonly) 11-beta-hydroxylase. The absence of these enzymes shifts production of adrenal enzymes to predominantly androgens, resulting in masculinization of both 46,XX and 46,XY patients (though the latter may be more subtle) and enlargement of the adrenal glands (fig. 3). **Most patients with 21-hydroxylase deficiency have a salt-wasting variant owing to mineralocorticoid deficiency; these patients, and those with 11-beta-hydroxylase deficiency, are less likely to be fertile. Exogenous administration of mineralocorticoids can reduce HPG axis suppression and restore fertility in some cases.**[52] Patients with rarer, more severe derangements of adrenal steroid synthesis (3-beta-hydroxysteroiddehydrogenase deficiency, StAR [steroidogenic acute regulatory] protein deficiency and abnormalities of cytochrome P450 enzymes) are typically considered infertile.

Transgender care. Gender-affirming health care in adolescents, including fertility preservation, is an evolving field. Most gender and sex-diverse adolescents would like to hear more about fertility preservation, and at least 25%–50% have a definite interest in fertility preservation.[53] However, only about 1 in 8 teens is counseled about fertility preservation, though more than a third of these patients choose to actively pursue fertility preservation techniques.[54] Cost as well as provider knowledge, comfort and the desire not to delay gender-affirming care are cited as reasons that counseling is not done.[54] Discussions surrounding fertility are time-sensitive as hormonal suppression of puberty will also disrupt the HPG axis; however, endogenous hormones may encourage the development of secondary sexual characteristics that are not aligned with the patient's identified gender, which can be emotionally distressing. Both oocyte cryopreservation and sperm banking are options, while gonadal cryopreservation (preservation of samples of whole gonadal tissue) is investigational.[55] Anatomical modifications with gender-affirming surgical techniques (eg phalloplasty, vaginoplasty, hysterectomy, gonadectomy) may also alter reproductive options.

Hypogonadism. Hypogonadism is the production of sex steroids by the gonad at levels insufficient to maintain normal endocrinological and sustentacular function. Hypogonadism is classified as hypergonadotropic or hypogonadotropic, depending on the location of the defect along the HPG axis. Measurements of early morning levels of GnRH, FSH, LH, and testosterone or estrogen typically distinguish between these types (table 3). Patients with hypogonadism should be thoroughly evaluated for underlying causes and sequelae (eg metabolic syndrome, osteoporosis).

Hypergonadotropic Hypogonadism: Congenital causes of hypergonadotropic hypogonadism include Klinefelter's syndrome, bilateral vanishing testes and Turner's syndrome; some of these conditions overlap with DSD. Acquired causes of hypergonadotropic hypogonadism include surgical removal of or traumatic damage to the gonads, infectious disease (eg mumps orchitis), drug exposure and deposition diseases (eg sarcoidosis, hemochromatosis).[56]

Klinefelter syndrome occurs in men with an additional X chromosome (47,XXY or 46,XY/47,XXY mosaic). **While the presentation is widely variable and can be subtle, men with Klinefelter syndrome are classically tall and thin, with small, firm testicles for age.** This abnormal testicular consistency reflects loss of testicular germ cells early in life (often before diagnosis) and associated testicular fibrosis.[57] Laboratory evaluation is typically congruent with hypergonadotropic hypogonadism. Semen analyses may show low or absent sperm production, consistent with the loss of normal testicular cells. Patients with sperm may be candidates for medically assisted reproduction; however, since the capability for sperm production is progressively lost over time, patients may need to consider banking sperm long before they desire to become parents. Therefore, the logistics of sperm banking, including cost, should be raised with the patient and family as early as possible. There remains considerable debate regarding the ethics of offering medically assisted reproduction to patients with Klinefelter syndrome, and genetic counseling should be routinely offered to patients and families during discussions about fertility.[58]

Patients with Turner syndrome have 45,XO or 45,XO/46,XX mosaic genotypes. These patients appear phenotypically female, with short stature, widely spaced nipples, and a webbed neck. Patients with Turner syndrome typically have streak gonads, with few to no ovarian follicles. (Streak gonads are also seen in patients with mixed gonadal dysgenesis, in whom the genotype is variable.) Exogenous

estrogen is needed to achieve sexual maturity at puberty. Patients with Turner syndrome can have successful pregnancies using donor oocytes and oocyte transfer; however, cardiovascular conditions associated with Turner syndrome (eg aortic coarctation) may necessitate more careful maternal and fetal monitoring during pregnancy.[59]

Loss of both gonads is extremely rare but occurs with bilateral vanishing testis (testicular regression syndrome) and bilateral testicular torsion. In testicular regression syndrome, the testes develop normally but are lost before birth, generally secondary to abnormal testicular blood flow because of infarction or torsion.[60] Patients with testicular regression syndrome have a nonpalpable gonad on the affected side, but typically have normal testicular histology on the contralateral (unaffected) side and so are typically virilized and appear phenotypically male.[61] However, testicular loss early in fetal development may be associated with lesser degrees of virilization. Surgical exploration will demonstrate an intact spermatic cord with blind-ending gonadal vessels and in many cases a small testicular remnant that microscopically shows hemosiderin-laden macrophages. **Because the secretion of LH and FSH is typically low in prepubertal children, measurements of anti-müllerian hormone and inhibin B (both secreted by Sertoli cells) may help distinguish between anorchia (low levels of both) and Sertoli cell-only syndrome (normal levels of both).[62]**

Hypogonadotropic Hypogonadism: The hallmark of hypogonadotropic hypogonadism is low serum gonadal and pituitary hormones. Pituitary damage can arise after trauma, cranial irradiation, infarction or tumors, or with deposition syndromes. Administration of hCG will generally promote testicular testosterone production. **Patients with suspected hypopituitarism should undergo measurement of other pituitary hormones (eg thyroid-stimulating hormone) and replacement if necessary.[63]**

Hypogonadotropic hypogonadism arising at the hypothalamic level is distinguished by low serum levels of hypothalamic, pituitary and gonadal hormones. It is most commonly due to direct hypothalamic damage from head trauma, cranial irradiation, stroke, extensive drug/alcohol exposure and deposition diseases.[64] The most common congenital hypothalamic conditions associated with hypogonadotropic hypogonadism are congenital hypogonadotropic hypogonadism and Prader-Willi syndrome.

Congenital hypogonadotropic hypogonadism with anosmia is known as Kallmann syndrome; it may be associated with new mutations or with X-linked or autosomal dominant inheritance with variable penetrance. The X-linked variant of Kallmann syndrome demonstrates abnormalities in anosmin-1, an extracellular glycoprotein encoded by the *KAL1* gene;[65] approximately a third of patients with a *KAL1* mutation also have unilateral renal agenesis. The autosomal dominant variant of the disease is more heterogeneous, with defects in multiple genes including *FGFR1, FGF8, PROKR2* and *PROK2*.[65] Patients with Kallmann syndrome should be evaluated for other midline fusion abnormalities (eg tooth agenesis).[66] **Some patients with Kallmann syndrome may produce sperm following combined hCG and FSH administration, although up to 2 years may pass before spermatogenesis occurs.[67]**

Prader-Willi syndrome occurs when a child inherits 2 copies of paternal chromosome 15, and none of the maternal chromosome 15 ("paternal imprinting"). In addition to hypogonadotropic hypogonadism, male children with Prader-Willi syndrome often have bilateral cryptorchidism requiring orchiopexy. Females with Prader-Willi syndrome may have primary ovarian dysfunction.[68]

Because the HPG axis is otherwise intact in patients with hypothalamic-level hypogonadotropic hypogonadism, treatment with GnRH/GnRH agonists is generally sufficient to promote pituitary gonadotropin secretion and subsequent gonadal hormone secretion. Initial treatment should center on attaining sufficient hormone levels for pubertal development, before fertility is considered. Some patients may require medically assisted reproduction in addition to hormonal therapy for successful conception. Patients with hereditary conditions should be offered genetic counseling prior to undertaking fertility-promoting treatments.

Treatment for pediatric cancer may be associated with the development of hypogonadotropic or hypergonadotropic hypogonadism and is discussed above.

Other conditions. While an exhaustive discussion of every possible cause of decreased fertility potential in children is beyond the scope of this Update, there are several conditions commonly encountered in pediatric urological practice that are associated with fertility challenges.

Spina Bifida: Patients with spina bifida may have decreased fertility potential secondary to neurological damage (eg erectile and ejaculatory dysfunction, abnormal genital sensation), impaired mobility or cryptorchidism. Patients with hydrocephalus are more likely to have alterations in fertility. The Spina Bifida Association has released guidelines for men's health issues in these patients.[69] While reproductive and sexual health in women with spina bifida is far less well studied, women with spina bifida indicate interest in learning more about these topics.[70] Patients with spina bifida with interest in conceiving children may benefit from a referral to a fertility specialist to discuss tailored treatment options (eg electroejaculation for ejaculatory dysfunction).

Cystic Fibrosis: Patients with cystic fibrosis may have multiple barriers to fertility. **Congenital bilateral absence of the vas deferens occurs in 97%–98% of males and is associated with obstructive azoospermia.** Thick cervical mucus may be a barrier to sperm. Patients with cystic fibrosis may also have hormonal abnormalities, though these are not well understood and may reflect multiple factors such as nutritional status.[71] Since both the vas and the kidney arise from the wolffian system, vasal anomalies should prompt consideration of renal agenesis. Partners of patients with presumptive cystic fibrosis should be offered screening prior to conception in order to facilitate genetic counseling.

Exstrophy-Epispadias Complex: Males are at increased risk for decreased fertility potential compared with female patients; in 1 study, only about 1 in 14 men had normal semen parameters.[72] Erectile and ejaculatory dysfunction may occur. Women may be at increased risk for pelvic organ prolapse, which may influence pregnancy outcomes.[73] The relationship of cystectomy and continent urinary diversion with fertility parameters is inconsistent.

RECOMMENDATIONS FOR UROLOGISTS

As noted earlier, deficits in patient and clinician knowledge of and comfort with fertility-related topics are associated with fewer discussions about fertility. Thus, we believe that the most important steps for urologists to take are to learn about fertility considerations in children and to talk about fertility early and often with patients at risk for decreased fertility potential.

Guidelines from multiple professional organizations, including the American Academy of Pediatrics, American Society for Reproductive Medicine, and the American Society of Clinical Oncology, stress the importance of discussion about the impact of disease and treatments on fertility and about options for management. Fertility preservation in children is often time-sensitive, requiring acquisition of tissue prior to starting treatment. This time sensitivity underscores the need for providers to have a baseline high level of comfort with and plan for initial discussions around fertility-related concerns in what can be an emotionally charged environment.

Formal fertility preservation programs are associated with greater use of patient satisfaction with fertility preservation techniques. The Pediatric Initiative Network of the Oncofertility Consortium brings together experts in pediatric reproductive endocrinology, oncology, urology, endocrinology, gynecology and mental health to inform recommendations for fertility-related care in children. **When fertility preservation is a standardized process integrated into routine care, the proportion of families receiving education about fertility-related care increases, as does their satisfaction with the process.**[74] These findings are especially relevant in light of the persistently low (25%–50%) rates of fertility preservation counseling in some studies and the disproportionate exclusion of children without insurance and those receiving "low risk" therapies from these discussions.[75]

Clinicians must also be aware of differences in fertility-related goals and values between parents and children, and in patients over time. In one study, most teenagers with cancer (80%) stated an interest in becoming biological parents, but just 31% considered parenthood a "top 3" life goal.[75] Similarly, parents charged with medical decision making for minor children may rely on their own values to inform their choices; these values may or may not align with those of their children.

CONCLUSIONS

Urologists should be aware of congenital and acquired medical conditions that may adversely affect fertility in children. Early identification and engagement of patients at risk for decreased fertility potential, ideally in a multidisciplinary setting, are critical to maximizing results.

DID YOU KNOW?

- Threats to fertility potential may occur in many congenital and acquired conditions in children and adolescents.
- Although a majority of adolescents seeking care for cancer, rheumatological disease or gender affirmation would like more information about fertility preservation, a minority actually receive counseling on this topic.
- The most common reasons that discussions about fertility potential are not initiated are lack of provider and patient comfort, lack of provider and patient knowledge and time sensitivity of medical and surgical treatment.
- Use of multidisciplinary fertility preservation programs and standardized processes for fertility preservation makes fertility preservation available to more patients and families and makes this a more satisfying process.

Table 1. Common pediatric causes of altered fertility potential relevant to urologists

	Causes	Mechanism	Management
Pediatric cancer and its treatments	Hormonal	Disruption of the HPG axis	Early counseling on fertility preservation options Assessment of HPG axis following oncologic treatment Some patients may benefit from hormonal therapy
	Structural	Disruption of normal anatomy and organ function by tumor or medical/surgical sequelae	Early counseling on fertility preservation options Some patients may benefit from medically assisted reproduction
		Direct cytotoxic effects on gonadal tissue from cancer therapy	Early counseling on fertility preservation options In some cases, male patients may experience recovery of spermatogenesis, and postpubertal patients should be encouraged to provide a semen sample for evaluation 2 or more years after the completion of therapy
Non-oncologic conditions treated with gonadotoxic therapies	Severe liver or kidney disease	Disruption of HPG axis	Early counseling on fertility preservation options Assessment of HPG axis following oncologic treatment Some patients may benefit from hormonal therapy
	Rheumatological diseases and their treatments	Hormonal alterations during disease flares Direct cytotoxic effects of medications	Early counseling on fertility preservation options In some cases, male patients may experience recovery of spermatogenesis, and postpubertal patients should be encouraged to provide a semen sample for evaluation 2 or more years after the completion of therapy
Cryptorchidism/ limited testicular reserve	Structural Hormonal Functional	Decrease in type Ad spermatogonia Normal serum FSH levels, but elevated compared with patients without cryptorchidism Normal sperm concentration and motility, but decreased compared with patients without cryptorchidism	Early orchiopexy (as soon as safely feasible, and ideally by one year of age) Patients with significant abnormalities in sperm structure and function that persist after orchiopexy may benefit from medically assisted reproduction
Varicocele	Locally increased testicular temperature Hormonal (possible)	Decreased sperm concentration and motility Evidence of oxidative stress Possibly altered serum levels of FSH, LH, inhibin B	Consider surgical repair of varicocele

Differences in sexual differentiation	Chromosomal anomalies with abnormal gonadal structure Variations in tissue sensitivity to hormonal stimulation resulting in structural and functional changes to gonads and reproductive organs	Klinefelter syndrome Turner syndrome Partial androgen insensitivity syndrome or CAIS	Early counseling on fertility preservation options specific to underlying medical condition Some patients may benefit from hormone administration
	Ovotesticular DSD 46,XY DSD males	Presence of both ovarian and testicular tissue Defects in testosterone synthesis or absent/ nonfunctional Leydig cells	
Congenital adrenal hyperplasia	Absent enzyme in steroid synthesis pathway	Increased androgen production and masculinization of external genitalia	Replacement of mineralocorticoid/glucocorticoid may improve fertility
Transgender care	Hormonal suppression of puberty Structural	Iatrogenic disruption of HPG axis Anatomical changes resulting from gender-affirming surgery	Discuss fertility preservation options (sperm banking, oocyte cryopreservation, investigational gonadal cryopreservation) with patients and families prior to initiating treatment
Hypergonadotropic hypogonadism	Kallmann syndrome Turner syndrome Gonadal damage or absence	Congenital disorder Infection Inflammation Deposition disorder Bilateral gonadal absence	For all: Perform complete evaluation for underlying etiology and sequelae Counsel patients on fertility preservation options early (as often fertility potential is lost over time) Some patients may benefit from medically assisted reproduction Genetic counseling for patient (and partner, if appropriate)
Hypogonadotropic hypogonadlism	Trauma Cranial irradiation Infarction Tumors Prader-Willi Stroke Drug/alcohol abuse Deposition syndromes		For all: Perform complete evaluation for underlying etiology and sequelae Correct secondary causes (tumors, deposition syndromes) if possible Counsel patients on fertility preservation options early (as often fertility potential is lost over time) Some patients may benefit from medically assisted reproduction Genetic counseling for patient (and partner, if appropriate)

Spina bifida	Cryptorchidism Impaired mobility Neurologic disorders		Consider surgical correction of physiological findings (eg cryptorchidism) that reduce fertility Consider counseling to help patients with mobility limitations and/or neurologic disorders explore options for sexual activity For all: Some patients may benefit from medically assisted reproduction
Cystic fibrosis	Obstructive azoospermia Extrinsic limitations on sperm motility Possible hormonal anomalies	Congenital bilateral absence of the vas deferens Thick secretions (eg cervical mucus) Perhaps related to nutritional status	Some patients may benefit from medically assisted reproduction Genetic counseling for patient (and partner, when appropriate) Consider options for improving nutritional status (eg supplements to augment absorption of fat-soluble vitamins)
Exstrophy-epispadias complex	Erectile and ejaculatory dysfunction Pelvic floor dysfunction	Congenital or acquired conditions (eg open bladder neck, abnormal neural function) Differences in pelvic floor anatomy and function intrinsic to exstrophy	Some patients may benefit from medically assisted reproduction or pharmacologic therapy Pelvic floor physical therapy

Table 2. Clinical grading of varicoceles

	Gross Visual Findings	Palpation of Venous Reflux	Typical Approximate Venous Diameter
Grade 1	Not visible	With Valsalva only	<10 mm
Grade 2	Minimally or not visible	With and without Valsalva	10–20 mm
Grade 3	Clearly visible	With and without Valsalva	>20 mm

Adapted from Dublin L and Amelar RD: Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril 1970; **21:** 606.

Table 3. Characteristics of hypergonadotropic and hypogonadotropic hypogonadism

	Hypergonadotropic	Hypogonadotropic	
Organ Primarily Affected	Gonad	Pituitary (anterior)	Hypothalamus
Serum GnRH Level	High	High	Low
Serum FSH and LH Level	High	Low	Low
Serum Sex Steroid Level	Low	Low	Low
Associated Congenital Conditions	Klinefelter syndrome, Turner syndrome	Empty sella syndrome	Congenital hypogonadotropic hypogonadism, Kallmann syndrome

Adapted from Fraietta et al.[64]

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine: Definitions of infertility and recurrent pregnancy loss. Fertil Steril, suppl., 2008; 90: S60.
2. Nahata LK, Ziniel SI, Garvey KC et al: Fertility and sexual function: a gap in training in pediatric endocrinology. J Pediatr Endocrinol Metabol 2017; 30: 3.
3. Zebrack BJ, Casillas J, Nohr L et al: Fertility issues for young adult survivors of childhood cancer. Psychooncology 2004; 13: 689.
4. Schilsky RL, Lewis BJ, Sherins RJ et al: Gonadal dysfunction in patients receiving chemotherapy for cancer. Ann Intern Med 1980; 93: 109.
5. Isaksson S, Bogefors K, Stahl O et al: High risk of hypogonadism in young male cancer survivors. Clin Endocrinol (Oxf) 2018; 88: 432.
6. Dillon KE and Gracia CR: Pediatric and young adult patients and oncofertility. Curr Treat Options Oncol 2012; 13: 161.
7. Wasilewski-Masker K, Seidel KD, Leisenring W et al: Male infertility in long-term survivors of pediatric cancer: a report from the childhood cancer survivor study. J Cancer Surviv 2014; 8: 437.
8. Garolla A, Pizzato C, Ferlin A et al: Progress in the development of childhood cancer therapy. Reprod Toxicol 2006; 22: 126.
9. Chow EJ, Stratton KL, Leisenring WM et al: Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol 2016; 17: 567.
10. Schover LR: Premature ovarian failure and its consequences: vasomotor symptoms, sexuality, and fertility. J Clin Oncol 2008; 26: 753.
11. Sanders JE, Hawley J, Levy W et al: Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996; 87: 3045.
12. Paix A, Antoni D, Waissi W et al: Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: a review. Crit Rev Oncol Hematol 2018; 123: 138.
13. Rivkees SA and Crawford JD: The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 1988; 259: 2123.
14. Izard MA: Leydig cell function and radiation: a review of the literature. Radiother Oncol 1995; 34: 1.
15. Meistrich ML, Chawla SP, Da Cunha MF et al: Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 1989; 63: 2115.
16. Webster KE, O'Bryan MK, Fletcher S et al: Meiotic and epigenetic defects in Dnmt3L-knockout mouse spermatogenesis. Proc Natl Acad Sci U S A 2005; 102: 4068.
17. Kobayashi H, Sato A, Otsu E et al: Aberrant DNA methylation of imprinted loci in sperm from oligospermic patients. Hum Mol Genet 2007; 16: 2542.
18. Shnorhavorian M, Schwartz SM, Stansfeld B et al: Differential DNA methylation regions in adult human sperm following adolescent chemotherapy: potential for epigenetic inheritance. PLoS One 2017; 12: e0170085.
19. Wo JY and Viswanathan AN: Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys 2009; 73: 1304.
20. Lobo RA: Potential options for preservation of fertility in women. N Engl J Med 2005; 353: 64.
21. Dillon KE and Gracia CR: Pediatric and young adult patients and oncofertility. Curr Treat Options Oncol 2012; 13: 161.
22. Kenney LB, Cohen LE, Shnorhavorian M et al: Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol 2012; 30: 3408.
23. Romerius P, Stahl O, Moell C et al: Hypogonadism risk in men treated for childhood cancer. J Clin Endocrinol Metab 2009; 94: 4180.
24. Ogilvy-Stuart AL, Clayton PE and Shalet SM: Cranial irradiation and early puberty. J Clin Endocrinol Metab 1994; 78: 1282.
25. de Jong PH and Dolhain RJ: Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin North Am 2017; 43: 227.
26. Eckersten D, Giwecman A, Pihlsgard M et al: Impact of kidney transplantation on reproductive hormone levels in males: a longitudinal study. Nephron 2018; 138: 192.
27. Brouwer J, Hazes JM, Laven JS et al: Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 2015; 74: 1836.
28. Provost M, Eaton JL and Clowse ME: Fertility and infertility in rheumatoid arthritis. Curr Opin Rheumatol 2014; 26: 308.
29. Alstead E: Fertility and pregnancy in inflammatory bowel disease. World J Gastroenterol 2001; 7: 455.
30. Christensen B: Inflammatory bowel disease and sexual dysfunction. Gastroenterol Hepatol (N Y) 2014; 10: 53.
31. Kokoszko-Bilska A, Sobkiewicz S and Fichna J: Inflammatory bowel diseases and reproductive health. Pharmacol Rep 2016; 68: 859.
32. Puchner R, Danninger K, Puchner A et al: Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception. Clin Exp Rheumatol 2012; 30: 765.
33. Massenkeil G, Alexander T, Rosen O et al: Long-term follow-up of fertility and pregnancy in autoimmune diseases after autologous haematopoietic stem cell transplantation. Rheumatol Int 2016; 36: 1563.
34. Chiodi S, Spinelli S, Bruzzi P et al: Menstrual patterns, fertility and main pregnancy outcomes after allogeneic haematopoietic stem cell transplantation. J Obstet Gynaecol 2016; 36: 783.
35. Carandang K, Mruk V, Ardoin SP et al: Reproductive health needs of adolescent and young adult women with pediatric rheumatic diseases. Pediatr Rheumatol Online J 2020; 18: 66.
36. Nahata L, Sivaraman V and Quinn GP: Fertility counseling and preservation practices in youth with lupus and vasculitis undergoing gonadotoxic therapy. Fertil Steril 2016; 106: 1470.
37. Ashley RA, Barthold JS and Kolon TF: Cryptorchidism: pathogenesis, diagnosis, treatment and prognosis. Urol Clin North Am 2010; 37: 183.
38. Kraft KH, Canning DA, Snyder HM 3rd et al: Undescended testis histology correlation with adult hormone levels and semen analysis. J Urol 2012; 188: 1429.
39. Rohayem J, Luberto A, Nieschlag E et al: Delayed treatment of undescended testes may promote hypogonadism and infertility. Endocrine 2017; 55: 914.
40. Ragab MW, Cremers J-F, Zitzmann M et al: A history of undescended testes in young men with Klinefelter syndrome does not reduce the chances for successful microsurgical testicular sperm extraction. Andrology 2018; 6: 525.
41. Meacham RB, Townsend RR, Rademacher D et al: The incidence of varicoceles in the general population when evaluated by physical examination, grayscale sonography and color Doppler sonography. J Urol 1994; 151: 1535.
42. Jockenhövel F, Gräwe A and Nieschlag E: A portable digital data recorder for long-term monitoring of scrotal temperatures. Fertil Steril 1990; 54: 694.
43. Diamond DA, Zurakowski D, Bauer SB et al: Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. J Urol 2007; 178: 1584.

44. Kirby EW, Wiener LE, Rajanahally S et al: Undergoing varicocele repair before assisted reproduction improves pregnancy rate and live birth rate in azoospermic and oligospermic men with a varicocele: a systematic review and meta-analysis. Fertil Steril 2016; 106: 1338.
45. Li F, Chiba K, Yamaguchi K et al: Effect of varicocelectomy on testicular volume in children and adolescents: a meta-analysis. Urology 2012; 79: 1340.
46. Cayan S, Sahin S, Akbay E. Paternity rates and time to conception in adolescents with varicocele undergoing microsurgical varicocele repair vs observation only: a single institution experience with 408 patients. J Urol 2017; 198: 195.
47. Fine RG, Gitlin J, Reda EF et al: Barriers to use of semen analysis in the adolescent with a varicocele: survey of patient, parental, and practitioner attitudes. J Pediatr Urol 2016; 12: e1.
48. Keene DJ, Fitzgerald CT and Cervellione RM: Sperm concentration and forward motility are not correlated with age in adolescents with an idiopathic varicocele and symmetrical testicular volumes. J Pediatr Surg 2016; 51: 293.
49. Damsgaard J, Joensen UN, Carlsen E et al: Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. Eur Urol 2016; 70: 1019.
50. Rutgers JL, Scully RE. The androgen insensitivity syndrome (testicular feminization): a clinicopathologic study of 43 cases. Int J Gynecol Pathol 1991; 10: 126.
51. Schultz BAH, Roberts S, Rodgers A et al: Pregnancy in true hermaphrodites and all male offspring to date. Obstet Gynecol 2009; 113: 534.
52. Yu RN and Diamond DA: Disorders of sexual development: etiology, evaluation, and medical management. In: Campbell-Walsh-Wein Urology. Partin AW, Dmochowski RR, Kavoussi LR, Peters CA, editors. 12th edition. Philadelphia, Pennsylvania: Elsevier; 2021: Chapter 48, pp. 990–1018.
53. Chen D, Matson M, Macapagal K et al: Attitudes toward fertility and reproductive health among transgender and gender-nonconforming adolescents. J Adolesc Health 2018; 63: 62.
54. Chen D, Simons L, Johnson EK et al: Fertility preservation for transgender adolescents. J Adolesc Health 2017; 61: 120.
55. Finlayson C, Johnson EK, Chen D et al: Proceedings of the working group session on fertility preservation for individuals with gender and sex diversity. Transgend Health 2016; 1: 99.
56. Ding J, Shang X, Zhang Z et al: FDA-approved medications that impair human spermatogenesis. Oncotarget 2017; 8: 10714.
57. Aksglaede L, Wikstrom AM, Rajpert-De Meyts E et al: Natural history of seminiferous tubule degeneration in Klinefelter syndrome. Hum Reprod Update 2006; 12: 39.
58. Franik S, Hoeijmakers Y, D'Hauwers K et al: Klinefelter syndrome and fertility: sperm preservation should not be offered to children with Klinefelter syndrome. Hum Reprod 2016; 31: 1952.
59. Karnis MF. Fertility, pregnancy, and medical management of Turner syndrome in the reproductive years. Fertil Steril 2012; 98: 787.
60. Pirgon O and Dundar BN: Vanishing testes: a literature review. J Clin Res Pediatr Endocrinol 2012; 4: 116.
61. Huff DS, Wu HY, Snyder HM 3rd et al: Evidence in favor of the mechanical (intrauterine torsion) theory over the endocrinopathy (cryptorchidism) theory in the pathogenesis of testicular agenesis. J Urol 1991; 146: 630.
62. Grinspon RP, Loreti N, Braslavsky D et al: Sertoli cell markers in the diagnosis of paediatric male hypogonadism. J Pediatr Endocrinol Metab 2012; 25: 3.
63. Kim SY: Diagnosis and treatment of hypopituitarism. Endocrinol Metab (Seoul) 2015; 30: 443.
64. Fraietta R, Zylberstejn DS and Esteves SC: Hypogonadotropic hypogonadism revisited. Clinics (Sao Paulo) 2013; 68: 81.
65. Dodé C and Hardelin J: Kallmann syndrome. Eur J Hum Genet 2009; 17: 139.
66. Bailleul-Forestier I, Gros C, Zenaty D et al: Dental agenesis in Kallmann syndrome individuals with FGFR1 mutations. Int J Paediatr Dent 2010; 20: 305.
67. Swee DS and Quinton R: Managing congenital hypogonadotropic hypogonadism: a contemporary approach directed at optimizing fertility and long-term outcomes in males. Endocrinol Metab 2019; 10: 2042018819826889.
68. Driscoll DJ, Miller JL, Schwartz S et al: Prader-Willi syndrome. In: GeneReviews. Adam MP, Ardinger HH, Pagon RA et al, editors. Seattle, Washington: University of Washington, Seattle; 2017: pp. 1993–2018.
69. Wiener JS, Frimberger DC and Wood H: Spina bifida health-care guidelines for men's health. Urology 2018; 116: 218.
70. Streur CS, Schafer CL, Garcia VP et al: "He told me it would be extremely selfish of me to even consider [having kids]": The importance of reproductive health to women with spina bifida and the lack of support from their providers. Disabil Health J 2020; 13: 100815.
71. Frayman KB, Chin M, Sawyer SM et al: Sexual and reproductive health in cystic fibrosis. Curr Opin Pulm Med 2020; 26: 685.
72. Reynaud N, Courtois F, Mouriquand P et al: Male sexuality, fertility, and urinary continence in bladder exstrophy-epispadias complex. J Sex Med 2018; 15: 314.
73. Rubenwolf P, Thomas C, Thuroff J et al: Sexual function and fertility of women with classic bladder exstrophy and continent urinary diversion. J Urol 2016; 196: 140.
74. Shnorhavorian M, Kroon L, Jeffries H et al: Creating a standardized process to offer the standard of care: continuous process improvement methodology is associated with increased rates of sperm cryopreservation among adolescent and young adult males with cancer. J Pediatr Hematol Oncol 2012; 34: e315.
75. Shnorhavorian M, Harlan LC, Smith AW et al: Fertility preservation knowledge, counseling, and actions among adolescent and young adult patients with cancer: a population-based study. Cancer 2015; 121: 3499.

Study Questions Volume 41 Lesson 5

1. Following solid organ (eg liver, kidney) transplantation normalization of alterations in the HPG axis typically occur after what time period?
   a. 1 month
   b. 6 months
   c. 1 year
   d. 2 years

2. The chemotherapeutic agent that most commonly causes gonadal damage is
   a. cisplatin
   b. bleomycin
   c. ifosfamide
   d. cyclophosphamide

3. Compared to normally descended testes, histological examination of undescended testicles shows
   a. decreased number of Ad spermatogonia
   b. decreased number of type B spermatogonia
   c. no change in the number of germ cells
   d. hypertrophic Leydig cells

4. A newborn male infant without any evidence of any other syndrome is born with an undescended testicle. In terms of maximizing fertility the best treatment is
   a. trial of hCG followed by orchiopexy after 6–12 months if the testicle doesn't descend
   b. trial of GnRH followed by orchiopexy after 3–6 months if the testicle doesn't descend
   c. orchiopexy prior to 1 year of age
   d. orchiopexy prior to 2 years of age

5. In terms of fertility preservation for the adolescent seeking gender-affirming care the patient should
   a. not be counseled as these patients are rarely interested in becoming parents
   b. be counseled early in the process of care
   c. be advised to delay hormonal therapy due to the impact on fertility
   d. be counseled to undergo gonadal cryopreservation as the most cost effective way to preserve fertility